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In re Application of: CARROLL, IAN

Title: TOXIN INDUCED SYMPATHECTOMY

Serial No.: 10/587,535
Examiner: Kolker, Daniel E

Filing Date: April 5, 2007
Group Art Unit: 1649

Mail Stop APPEAL
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

I. REAL PARTY IN INTEREST

The real party in interest is The Board of Trustees of Leland Stanford Junior University, to which all rights have been assigned.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-10 and 12 are pending.

Claims 1-10 and 12 stand rejected and are appealed herein.

IV. STATUS OF AMENDMENTS

Claims 1, 4, 8, 9, 10 and 12 were amended in the Response mailed March 14, 2008, and the amendments entered as noted in the Office Action mailed June 24, 2008. No further amendments were made to the claims. All amendments have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of independent claim 1 relates to a method for treating sympathetically maintained chronic pain, the method comprising administering by percutaneous injection (page 7, lines 33-34) a therapeutically effective dose (page 7, lines 12-20) of a botulinum toxin type A, B, C₁, D, E, F or G (page 7, lines 1-2) to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time (page 8, lines 14-18). In some embodiments (Claim 2), the botulinum toxin is type A (page 7, line 2). In some embodiments (Claim 3), the effective dose of botulinum toxin is from about 1 to 300 units (page 7, lines 21-27). In one embodiment (Claim 5), the sympathetically maintained chronic pain is of the upper extremities, and the block is of the inferior, middle or superior cervical sympathetic ganglion (page 8, lines 2-3). In one embodiment (Claim 6), the sympathetic ganglion is one or more of the superior cervical ganglia; middle superior cervical ganglion; vertebral ganglion; cervicothoracic (stellate) ganglion; sympathetic trunk; thoracic sympathetic ganglion; aorticorenal ganglion; lumbar sympathetic ganglion; celiac ganglion; superior mesenteric ganglion; inferior mesenteric ganglion; superior and inferior hypogastric plexus; and ganglion impar (page 7, line 36 – page 8, line 2). In one embodiment (Claim 7), the method further comprises the steps of identifying the chronic pain as being mediated by the sympathetic nervous system by administering a local anesthetic as a sympathetic block (page 8, lines 20-26), wherein a cessation of at least about 50% of the perceived pain for a short period of time following the sympathetic block is indicative of sympathetically maintained pain (page 11, lines 7-12).

The subject matter of independent claim 4 relates to a method for treating sympathetically maintained chronic pain of the lower extremities, the method comprising administering by percutaneous injection (page 7, lines 33-34) from about 1 to 300 units (page 7, lines 21-27) of botulinum toxin type A (page 7, line 2) to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block of the lumbar splanchnic nerves and decreasing sympathetically maintained chronic pain of the lower extremities (page 10, line 37 – page 11, line 1).

The subject matter of independent claim 8 relates to a method for treating cardiovascular conditions, the method comprising administering by percutaneous injection (page 7, lines 33-34) a therapeutically effective dose of a botulinum toxin type A, B, C₁, D, E, F or G (page 7, lines 1-2) to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time (page 8, lines 14-18). The cardiovascular condition is selected from the group consisting of retinal artery thrombosis; cerebral vasospasm, peripheral vascular disease; coronary artery disease; post prandial ischemia; Raynaud's Disease, and Raynaud's Phenomenon (page 11, line 30 – page 12, line 20).

The subject matter of independent claim 9 relates to a method for treating peripheral vascular disease in a patient, the method comprising administering by percutaneous injection (page 7, lines 33-34) a therapeutically effective dose of botulinum toxin type A to a sympathetic ganglion of a human patient suffering from peripheral vascular disease (page 11, line 32-33), thereby achieving a sympathetic block for an extended period of time and increasing blood flow to peripheral vasculature (page 11, lines 27-29). In one embodiment (Claim 10), the treatment additionally provides for pain relief in the patient (page 14, lines 30-35). In one embodiment (Claim 12), the effective dose of botulinum toxin is from about 1 to 300 units (page 7, lines 21-27).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are 4 grounds for rejection of the claims:

I) Claims 1-3 and 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim ((2002) Autonomic Neuroscience 102:8-12) in view of Donovan (U.S. Patent Application Publication 2001/0023243).

II) Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243, and further in view of Erickson ((1993) Radiology 188:707-709).

III) Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275).

IV) Claims 1-3, 5-6, 8-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henrard ((1982) Arch Mal Coeur 75(11):1317-1320) in view of Kim (2002) and Donovan 2001/0023243.

VII. ARGUMENT

I) Claims 1-3 and 5-6 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kim ((2002) Autonomic Neuroscience 102:8-12) in view of Donovan (U.S. Patent Application Publication 2001/0023243). In making this rejection, the Examiner has asserted that Kim *et al.* teach administration of botulinum toxin type A, recited in claims 1 and 2, that the dose used was 2-10 units per kilogram of body weight, administered to rabbits, which is within the range recited in claim 3, given that rabbits weigh less than 30 kg, and administration to the superior cervical ganglion

as recited in claim 5-6. The Examiner concedes that "Kim does not teach administration to humans, and does not explicitly teach percutaneous injection."

The instant application teaches a method for treating sympathetically maintained chronic pain, the method comprising administering by percutaneous injection a therapeutically effective dose of a botulinum toxin type A, B, C₁, D, E, F or G to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time. Appellants submit that Kim *et al.* fail to teach a method of treating a human by "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time".

In contrast to the methods of the present claims, Kim *et al.* teaches a method of administering botulinum toxin A to the superior cervical ganglion to selectively kill nerves in a rabbit (the Examiner notes in the Final Office Action at page 4, second paragraph, that Kim *et al.* teaches the use of BTA as a "neurolytic agent"). The methods of the cited art thus do not teach a sympathetic block, but rather a destruction of nerve cells.

The Examiner argues that Kim *et al.* use the term neurolytic to refer to agents that decrease neural activity, not those that kill neurons. Applicants note, however, that the dictionary definition of neurolysis (The American Heritage® Medical Dictionary Copyright © 2007, 2004 by Houghton Mifflin Company) is:

1. The breaking down or destruction of nerve tissue, especially as a result of disease.
2. The surgical freeing of a nerve from inflammatory adhesions.

Kim *et al.*, in fact, discuss neurolytic agents and note that "alcohol and phenol compounds destroy nerve fibers nonselectively" (page 8, first paragraph). Thus the art and the specific reference teach away from the Examiner's interpretation, and teach that a neurolytic agent is one that destroys nerve tissue.

Appellants further submit that Kim *et al.* fails to teach the use of a botulinum toxin in treating sympathetically maintained chronic pain. The methods of Kim *et al.* involve surgically opening the neck region of a rabbit, and perfusing the superior cervical ganglion with botulinum toxin. This procedure is then evaluated by determining whether it has induced miosis, *i.e.* constriction of the pupil of the eye. The effect of the procedure is compared to animals where the ganglion was removed completely. The Examiner has asserted that it would have been obvious to one of ordinary skill in the art to modify the methods of Kim *et al.* to treat humans in pain.

Appellants submit that Kim *et al.* does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain. Rather, Kim *et al.* simply teaches a utility for botulinum toxin in inducing miosis, and provides no prediction of success for the use of botulinum toxin in treating sympathetically maintained chronic pain.

Appellants further note that Kim *et al.* found a “lack of a close agreement between the botulinum toxin injection and resultant occurrence of miosis” (p. 11, col. 2, l. 8-10 of Kim *et al.*)

The Examiner asserts in the Office Action and Final Office Action that Kim *et al.* teaches that “[s]ympathetic block is one of the most important methods of treating chronic pain” (Kim *et al.*, p. 8, line 1, cited by Examiner in Final Office Action, P. 4, l. 10), that the miosis measured by Kim is a way to determine the functioning of the superior cervical ganglion (Final Office Action, p. 4, l. 15-16), that Kim measured miosis following injection of botulinum toxin into the ganglion in order to determine the degree to which the toxin blocks sympathetic ganglion activity (Final Office Action, p. 4, l. 20-22), that Kim concluded that “botulinum toxin acted on the sympathetic neurons of the SCG” (Kim *et al.* p. 11, second paragraph) and therefore “botulinum toxin has usefulness as a neurolytic agent for sympathetically mediated pain” (Kim *et al.*, p. 11, final sentence).

The Appellants argue that the scientific art at the time of the present invention teaches away from correlations between pupil dilation and measurements of the reduction of chronic pain in other animal models.

A publication submitted to the Patent Office in Applicant’s response filed March 14, 2008 stated that: “because different neurotransmitters are involved in pupil and pain mechanisms of antidepressant drugs, it is difficult to evaluate the analgesic response with the pupil diameter.” (Onal *et al.* Gen Pharmacol. 1999 Jul;33(1):83-9). Therefore, in the absence of a teaching of a correlation between i) extent of block in sympathetic ganglion activity and extent of pupil dilation, and ii) extent of block of sympathetic ganglion activity and relief from chronic pain, there would be no way for the ordinarily skilled artisan to predict from pupil measurements if a method developed to block sympathetic ganglion activity so as to induce miosis will also treat chronic pain. Indeed, the degree to which one must block sympathetic ganglion activity to promote miosis may very well be entirely different from the degree (if any, short of neurolytic treatment) to which one must block sympathetic ganglion activity to treat chronic pain.

Kim *et al.* makes no claim of a correlation between their studies on miosis and the relief of sympathetic pain, much less a claim that their studies might provide a method of the extent to which the sympathetic ganglion must be blocked in order to relieve chronic pain. Kim *et al.* postulates upon the possibility, but provides no enabling guidance to provide a reasonable expectation of

success, (keeping in mind Kim *et al.*'s stated lack of close agreement between the toxin injection and miosis). Thus, since no chronic pain studies were performed by Kim *et al.* and no correlations between the effects of sympathetic block on pupil dilation and on chronic pain were made by Kim *et al.*, Kim *et al.* does not make obvious that chronic pain would be successfully treated by botulinum toxin.

The Examiner has argued in response to this citation of Onal that:

While animal models of pain may not be fully predicative of success in humans, there is no particular reason to doubt that the findings of Kim *et al.* could be extended to humans. The finding that botulinum toxin inhibits activity of the superior cervical ganglion in rabbits could reasonably be extended to humans based upon the similar anatomy. Additionally, absolute success is not required in determination of obviousness, rather the standard is a reasonable expectation of success; see MPEP 2143.02(I) (Final Office Action, p. 5, l. 7-12).

Further, the Examiner notes that "it is clear that Onal uses intravenous injections. This route is not the same as claimed and would be expected to have quite different effects" (Final Office Action, p. 5, l. 15-17).

The Appellants submit the above-cited facts from Onal (see above) i.e. it is difficult to evaluate the analgesic response with the pupil diameter, are applicable to the instant application regardless of the differences between Onal's techniques and those of the instant application, as are the conclusions that may be drawn from Onal, i.e. that since no chronic pain studies were performed by Kim *et al.*, and hence no correlations between effects on pupil dilation and on chronic pain were made by Kim *et al.*, Kim *et al.* does not make obvious that chronic pain would be successfully treated by botulinum toxin.

Furthermore, Appellants have previously provided arguments that even assuming, *arguendo*, that Kim *et al.* taught a method of blocking sympathetic activity to reliably and consistently induce miosis in rabbits, and even if Kim *et al.* taught a correlation between inducing miosis and pain relief in animals, one of skill in the art would still not reasonably extend such findings in the rabbit to the treatment of neuropathic pain in humans.

It is well understood in the art that animal models for neuropathic pain are not necessarily predictive of human behavior. As explained by Campbell and Meyer (2006) Neuron 52:77-92:

Animal models of neuropathic pain in some cases have been inconsistent with human models. Allodynia in painful diabetic neuropathy in humans is infrequent yet appears to be robust in rat models. NK1 antagonists appeared to have promise for treatments of pain based on animal models yet to date have not proven useful in patients. Vierck (2006) argues that "reflex" measures of pain in animal neuropathic models are intrinsically flawed and are neither sensitive nor specific predictors of drug efficacy in man. For example, he points out that the paw withdrawal threshold method tests motor neuron response rather than simply providing a measure of pain. Moreover, he indicates that rostral signaling pathways may be ignored when one merely measures the paw-withdrawal threshold.

Thus, one of skill in the art would have no reasonable expectation of success in the treatment of human neuropathic pain from results of studies in animal models such as those by Kim *et al.*

Appellants further submit that Kim *et al.* neither teaches nor makes obvious a method for providing "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", because the method of achieving a sympathetic block as taught by Kim *et al.* is unreliable even for rabbits.

For example, Kim *et al.* found that all of the rabbits in their study that had been given 10 U of botulinum toxin died. Furthermore, "a 30% responsiveness was seen in the 2 U group (3/10), and 35% responsiveness in the 5 U group" (p. 9, col. 2, l. 16-20) and "significant variation was found in terms of the onset time and duration of miosis" (p. 9, col. 2, l. 25-26). And as cited above, Kim *et al.* found a "lack of a close agreement between the botulinum toxin injection and resultant occurrence of miosis".

Appellants note here that the presence or absence of papillary constriction (miosis) was determined by review of an investigator – no measurements were taken to provide quantitative data.

Thus, Kim *et al.* does not teach a dose of botulinum toxin that, when provided to a rabbit, can reliably and consistently block the sympathetic ganglion without killing the rabbit, much less a close agreement between the amount of botulinum toxin injected and the onset, duration and extent of miosis that one ordinarily skilled in the art might predict to observe in a rabbit, much less in a human.

Thus, Appellants respectfully submit that in light of such a lack of such enabling support, and in light of the lack of rigor in their assessment of results (for example the lack of quantitative data), Kim *et al.* does not teach a method of administering "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion," even to a rabbit, much less to a human.

Thus, the Appellants submit that Kim *et al.* does not teach "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient", and does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain.

The Appellants submit that Donovan does not remedy the deficiencies of Kim *et al.*, because Donovan does not teach nor make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain. Rather, Donovan teaches a method for treating hyperparathyroidism and/or hypercalcemia by local administration of botulinum toxin to a sympathetic ganglion which innervates a parathyroid hormone secreting parathyroid cell.

The Examiner argues in the Final Office Action, p. 5, l. 24-28, that "given that Donovan teaches that blocking sympathetic ganglia with other agents is known to treat pain (see paragraph 0090), and that Donovan also teaches that certain other conditions (e.g. thyroid disease) can be treated by percutaneous administration of botulinum toxin to the ganglia, the artisan of ordinary skill would have had a reasonable expectation of success in administering this toxin to the appropriate ganglia for treatment of pain.

The Appellants submit that the teachings in Donovan on blocking sympathetic ganglia with other agents to treat pain (paragraph 0090) do not make obvious the claims of the instant application because they are with regard to the use of neurolytic agents such as ethanol and phenol (paragraph 0090), which act broadly and exert their effects by neurolytic mechanisms (specification, p.2, l.20-21). The present application notes that "When a neurolytic agent is used, axonal damage results leading to unpredictable regrowth of the nerves. Additionally, significant scarring in the area occurs, which limits the ability to perform repeated neurolytic blocks. Finally, spread of the neurolytic solution can occur to other structures leading to significant neurological or vascular injury."

In contrast, botulinum toxin exerts its effects by blocking the release of acetylcholine from preganglionic neurons. The mechanism of action is different, as are the nerves primarily affected by the therapeutic. Thus, whereas the artisan of ordinary skill following the teachings of Donovan would not have had a reasonable expectation of success in administering botulinum toxin to the appropriate ganglia for treatment of chronic pain.

The Appellants submit that the teachings of Donovan that certain other conditions can be treated by percutaneous administration of botulinum toxin to the ganglia also would not provide the ordinarily skilled artisan with a reasonable expectation of success in administering botulinum toxin to ganglia for treatment of pain, because no correlation exists in the art between the nature and extent of a sympathetic block required to treat these certain other conditions and the nature and extent of a sympathetic block (if any, short of neurolytic treatment) that might be required to treat chronic pain.

Donovan makes no claim of a correlation between their studies on relief of hyperparathyroidism or hypercalcemia and the relief of sympathetic pain, much less a claim that their studies might provide a method of the extent to which the sympathetic ganglion must be blocked in order to relieve chronic pain. Since no chronic pain studies were performed by Donovan, and no correlations between the extent of sympathetic block required to treat hyperparathyroidism and the extent of sympathetic block required to relieve chronic pain were reported by Donovan or in the art at the time of the instant invention, Donovan does not make obvious the utility for botulinum toxin in treating sympathetically maintained chronic pain.

Reconsideration and withdrawal of the rejection of the claims on this ground under 35 U.S.C. 103(a) is respectfully requested.

II) Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243, and further in view of Erickson ((1993) Radiology 188:707-709).

Appellants respectfully submit that Kim *et al.* fails to teach "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", and does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain, for the reasons set forth above.

As argued above in response to the Examiner's first rejection, Appellants agree with the Examiner that Kim *et al.* does not teach "administering by percutaneous injection". Rather, Kim *et al.* teaches surgical dissection and perfusion of the nerve, which are methods directed at neurolytic techniques.

Appellants submit that Donovan fails to remedy the deficiencies of Kim *et al.* because Donovan does not teach nor make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain, as discussed above in response to the Examiner's first rejection.

Appellants submit that Erickson fails to remedy the deficiencies of Kim *et al.* in view of Donovan. While the use of a local anesthetic to achieve a temporary block is known in the art, as evidenced by Erickson, such knowledge does not teach or suggest the use of botulinum toxin for treating sympathetically maintained chronic pain.

Erickson teaches administration of a local anesthetic as a sympathetic block. The active agents utilized by Erickson *et al.* include Bupivacaine and Lidocaine, which bind to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, preventing depolarization. In contrast, the methods of the present invention provide for a selective block of acetylcholine release from the preganglionic neurons. Thus, the mechanism of action is different, as are the nerves primarily affected by the therapeutic agent. These are important distinctions in a method where a selective block of the nerve function is used to "short-circuit" the cycle in which sympathetic pain is maintained. The methods of the prior art do not achieve this same effect.

As such, the Appellants maintain that the teachings of Erickson for the use of depolarization blockers to treat chronic pain would not have provided the ordinarily skilled artisan with a reasonable expectation of success for using the acetylcholine release blocker botulinum toxin in treating

sympathetically maintained chronic pain, and therefore would not remedy the deficiencies of Kim *et al.* and Donovan.

The Examiner states that "it would have been obvious to one of ordinary skill in the art to include the step of administering a short-acting local anesthetic as a sympathetic block, as taught by Erickson, when performing the methods of claims 1-3, thereby arriving at the invention of claim 7" (Final Office Action, p.6, l.14-17) The Appellants argue, however, that in the absence of references that teach the utility for botulinum toxin in treating sympathetically maintained chronic pain, the method of claim 1, which claim 7 depends upon, is not made obvious. Thus, the combination of references does not make the instant invention obvious.

Reconsideration and withdrawal of the rejection of the claims on this ground under 35 U.S.C. 103(a) is respectfully requested.

III) Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) in view of Donovan 2001/0023243, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275).

Appellants respectfully submit that Kim *et al.* fails to teach "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", and does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain, for the reasons set forth above.

As argued above in response to the Examiner's first rejection, Appellants agree with the Examiner that Kim *et al.* does not teach "administering by percutaneous injection". Rather, Kim *et al.* teaches surgical dissection and perfusion of the nerve, which are methods directed at neurolytic techniques.

Appellants submit that Donovan fails to remedy the deficiencies of Kim *et al.* because Donovan does not teach nor make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain, as discussed above in response to the Examiner's first rejection. While the use of an anesthetic

Appellants submit that Brushey fails to remedy the deficiencies of Kim *et al.* in view of Donovan, because Brushey does not teach or make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain.

As stated by the Examiner, Brushey "teaches that the splanic nerve should be blocked when pain is in the lower extremities, by blocking the celiac plexus (Brushey paragraphs 1-4).

However, Brushey does not teach administration of botulinum toxin as recited in claim 1" (Final Office Action, p. 7, L. 15-17).

Appellants submit that Kim *et al.* in view of Donovan does not teach or make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain. Appellants concur with the Examiner that Brushey does not teach this element, either. Thus, Appellants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention.

Reconsideration and withdrawal of the rejection of the claims on this ground under 35 U.S.C. 103(a) is respectfully requested.

IV) Claims 1-3, 5-6, 8-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henrard ((1982) Arch Mal Coeur 75(11):1317-1320) in view of Kim (2002) and Donovan 2001/0023243.

Appellants submit that Henrard *et al.* does not teach the methods of the instant application of treating a human by "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", or a utility for botulinum toxin in treating sympathetically maintained chronic pain (independent claim 1), cardiovascular conditions (independent claim 8), or peripheral vascular disease (independent claim 9). Rather, Henrard *et al.* teaches the use of homolateral thoracic sympathectomy to treat coronary vasospasm.

In making this rejection, the Examiner states that "the deficiency of Henrard *et al.* (administration of botulinum toxin to inactivate sympathetic ganglia rather than surgical removal to inactivate for treatment of the coronary vasospasm) is cured by Kim. . . . Kim teaches that botulinum toxin, when injected into sympathetic ganglion, is sufficient to inactive it. Additionally, Donovan provides guidance to select the percutaneous injection route now claimed, as he teaches that this is an effective way to administer this toxin to the ganglia" (Final Office Action, p. 9, l. 1-6).

Appellants submit that the method of Henrard *et al.*, i.e. homolateral thoracic sympathectomy (the surgical removal of a sympathetic ganglion), is a highly invasive procedure that produces an extensive global effect, because the procedure axotomizes all neurons that synapse at the removed ganglion. In contrast, the method of the instant application, percutaneous injection of an agent that targets a particular biochemical pathway, is a refined approach that impacts only that biochemical pathway, while leaving the neurons and other biochemical pathways intact.

Thus, Appellants submit that achieving a sympathetic block by sympathectomy so as to treat a cardiovascular disease would not provide one ordinarily skilled in the art with any reasonable

expectation of success in the treatment of cardiovascular disease with a finely targeted method such as that of the instant application.

Appellants submit that Kim *et al.* does not remedy any deficiencies of the Henrard *et al.* because Kim *et al.* also does not teach "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", or a utility for botulinum toxin in treating sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease.

The Examiner states that Kim *et al.* cures the deficiencies of Henrard *et al.* because "Kim teaches that botulinum toxin, when injected into sympathetic ganglion, is sufficient to inactive it." As argued above in response to the Examiner's first rejection, Appellants submit that Kim *et al.* neither teaches nor makes obvious a method for providing "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time", because the method of achieving a sympathetic block as taught by Kim *et al.* and recited by the Examiner is unreliable, even for rabbits.

Kim *et al.* does not teach a dose of botulinum toxin that, when provided to a rabbit, can reliably and consistently block the sympathetic ganglion without killing the rabbit, much less a close agreement between the amount of botulinum toxin injected and the onset, duration and extent of miosis that one ordinarily skilled in the art might predict to observe in a rabbit, much less in a human. Thus, Appellants respectfully submit that in light of such a lack of such enabling support, and in light of the lack of rigor in their assessment of results, Kim *et al.* does not teach a method of administering "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion," even to a rabbit, much less to a human.

Appellants submit that Kim *et al.* does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease. Rather, Kim *et al.* simply teaches a utility for botulinum toxin in inducing miosis, and provides no prediction of success for the use of botulinum toxin in treating these other conditions. Kim *et al.* makes no claim of a correlation between their studies on miosis and the relief of these other conditions, much less a claim that their studies might provide a method of the extent to which the sympathetic ganglion must be blocked in order to relieve these other conditions. Kim *et al.* postulates upon the possibility of relief of chronic pain, but provides no enabling guidance to provide a reasonable expectation of success. Thus, Kim *et al.* does not make obvious that any of these conditions would be successfully treated by botulinum toxin.

Thus, the Appellants submit that Kim *et al.* does not teach "administering by percutaneous injection" "a therapeutically effective dose of a botulinum toxin . . . to a sympathetic ganglion of a human patient", and does not teach a utility for botulinum toxin in treating sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease.

The Examiner states that Donovan cures the deficiencies of Henrard *et al.* in view of Kim *et al.* because "Donovan provides guidance to select the percutaneous injection route now claimed, as he teaches that this is an effective way to administer this toxin to the ganglia". Appellants agree that Donovan teaches percutaneous injection. However, Appellants submit that Donovan does not remedy the deficiencies of Henrard *et al.* in view of Kim *et al.* because Donovan does not teach nor make obvious a utility for botulinum toxin in treating sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease. Rather, Donovan teaches a method for treating hyperparathyroidism and/or hypercalcemia by local administration of botulinum toxin to a sympathetic ganglion which innervates a parathyroid hormone secreting parathyroid cell.

As argued above in response to the Examiner's first rejection, the Appellants submit that the teachings of Donovan on blocking sympathetic ganglia with other agents to treat pain (paragraph 0090) do not make obvious the claims of the instant application because they are with regard to the use of neurolytic agents such as ethanol and phenol (paragraph 0090), which act broadly and exert their effects by neurolytic mechanisms (specification, p.2, 1.20-21). In contrast, botulinum toxin exerts its effects by blocking the release of acetylcholine from preganglionic neurons. The mechanism of action is different, as are the nerves primarily affected by the therapeutic. Thus, whereas the artisan of ordinary skill following the teachings of Donovan might have had a reasonable expectation of success in treating chronic pain with a neurolytic agent, the artisan would not have had a reasonable expectation of success in administering botulinum toxin to the appropriate ganglia for treatment of chronic pain, cardiovascular conditions, or peripheral vascular disease.

As also argued above, the Appellants submit that the teachings of Donovan that certain other conditions can be treated by percutaneous administration of botulinum toxin to the ganglia would not provide the ordinarily skilled artisan with a reasonable expectation of success in administering botulinum toxin to ganglia for treatment of sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease, because no correlation exists in the art between the nature and extent of a sympathetic block required to treat the conditions of Donovan and the nature and extent of a sympathetic block (if any, short of neurolytic treatment, as taught by Donovan, or sympathectomy, as taught by Henrard *et al.*) that might be required to treat sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease.

Thus, Donovan does not teach or make obvious the utility for botulinum toxin in treating sympathetically maintained chronic pain, cardiovascular conditions, or peripheral vascular disease, and does not remedy the deficiencies of Henrard *et al.* in view of Kim *et al.*

Appellants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Reconsideration and withdrawal of the rejection of the claims on this ground under 35 U.S.C. 103(a) is respectfully requested.

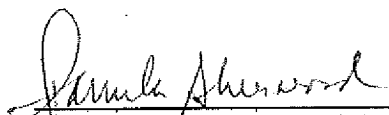
CONCLUSION

Appellants respectfully request that each of the rejections of claims be reversed and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

The appropriate fee is either attached or authorized. If the Commissioner determines that an additional fee is necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication or credit any overpayment to Deposit Account No. **50-0815**.

Respectfully submitted,
BOZICEVIC, FIELD AND FRANCIS LLP

Date: October 15, 2008


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VIII. CLAIMS APPENDIX

The claims on appeal are as follows:

1. A method for treating sympathetically maintained chronic pain, the method comprising:
administering by percutaneous injection a therapeutically effective dose of a botulinum toxin type A, B, C₁, D, E, F or G to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time.
2. The method according to Claim 1, wherein said botulinum toxin is botulinum toxin type A.
3. The method according to Claim 2, wherein said effective dose of botulinum toxin is from about 1 to 300 units.
4. A method for treating sympathetically maintained chronic pain of the lower extremities, the method comprising:
administering by percutaneous injection from about 1 to 300 units of botulinum toxin type A to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block of the lumbar splanchnic nerves and decreasing sympathetically maintained chronic pain of the lower extremities.
5. The method according to Claim 3, wherein said sympathetically maintained chronic pain is of the upper extremities, and said block is of the inferior, middle or superior cervical sympathetic ganglion.
6. The method according to Claim 3, wherein said sympathetic ganglion is one or more of the superior cervical ganglia; middle superior cervical ganglion; vertebral ganglion; cervicothoracic (stellate) ganglion; sympathetic trunk; thoracic sympathetic ganglion; aorticorenal ganglion; lumbar sympathetic ganglion; celiac ganglion; superior mesenteric ganglion; inferior mesenteric ganglion; superior and inferior hypogastric plexus; and ganglion impar.
7. The method according to Claim 3, wherein said method further comprises the steps of:
identifying the chronic pain as being mediated by the sympathetic nervous system by administering a local anesthetic as a sympathetic block;

wherein a cessation of at least about 50% of the perceived pain for a short period of time following said sympathetic block is indicative of sympathetically maintained pain.

8. A method for treating cardiovascular conditions, the method comprising:
administering by percutaneous injection a therapeutically effective dose of a botulinum toxin type A, B, C₁, D, E, F or G to a sympathetic ganglion of a human patient, thereby achieving a sympathetic block for an extended period of time, wherein said cardiovascular condition is selected from the group consisting of retinal artery thrombosis; cerebral vasospasm, peripheral vascular disease; coronary artery disease; post prandial ischemia; Raynaud's Disease, and Raynaud's Phenomenon.

9. A method for treating peripheral vascular disease in a patient, the method comprising:
administering by percutaneous injection a therapeutically effective dose of botulinum toxin type A to a sympathetic ganglion of a human patient suffering from peripheral vascular disease, thereby achieving a sympathetic block for an extended period of time and increasing blood flow to peripheral vasculature.

10. The method according to Claim 9, wherein said treatment additionally provides for pain relief in said patient.

12. The method according to Claim 9, wherein said effective dose of botulinum toxin is from about 1 to 300 units.

IX. EVIDENCE APPENDIX

There are no Exhibits.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.